Metabolic markers for mitochondrial function

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DESCRIPTION (provided by applicant):	ABSTRACT Mitochondrial (MT) dysfunction is a factor in numerous chronic diseases and the toxicity related to environmental exposures, but early deficits in MT function are difficult to detect. Current clinical markers for mitochondrial dysfunction typically detect only advanced symptoms of tissue injury and disease, yet the sensitivity to detect mild MT dysfunction and heterogeneity within tissue has hampered robust identification of meaningful biomarkers at early stages. Mitochondrial biology is variable; and chronic, low level MT dysfunction may be below the detection sensitivity of many techniques. We need new tools to enhance the mechanistic understanding of environmentally-induced mitochondrial toxicity at early stages to enable prevention and intervention. To address this problem, we have developed and applied a new technology for single cell mass spectrometry, called Nanostructure-Initiator Mass Spectrometry (NIMS). NIMS has both the single cell resolution (1-10 m) and the high sensitivity (attomolar) needed to detect early biomarkers of MT dysfunction as metabolic "signatures" in individual cells. NIMS offers a number of advantages over standard mass spectrometry, including (1) ultra-high sensitivity, (2) high selectivity, and (3) single cell resolution to reduce sample complexity. We apply NIMS to identify metabolic signatures for early MT dysfunction in the brain and blood of diseased animals or animals treated with environmental toxins at "subclinical" levels. In Aim 1, we use NIMS to generate metabolic signatures for MT decline. In Aim 2, we will functionally test whether the biomarker reflects functional changes in MT or MT within the context of the cell. NIMS can be applied to any tissue and any cell type, to quantitatively sort out complex changes that occur in dynamic cellular environments, and minimizes the inherent system heterogeneity that has confounded efforts in detecting meaningful markers of MT decline.
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